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Molecular Size as the Main Determinant of Solute Maximum Flux Across the Skin

Beatrice M. Magnusson, Yuri G. Anissimov, Sheree E. Cross, and Michael S. Roberts
Therapeutics Research Unit, Department of Medicine, University of Queensland, Princess Alexandra Hospital, Brisbane, Australia

One of the most important determinants of dermatological and systemic penetration after topical application is the delivery or flux of solutes into or through the skin. The maximum dose of solute able to be delivered over a given period of time and area of application is defined by its maximum flux (J_{max}, mol per cm^2 per h) from a given vehicle. In this work, J_{max} values from aqueous solution across human skin were acquired or estimated from experimental data and correlated with solute physicochemical properties. Whereas epidermal permeability coefficients (k_p) are optimally correlated to solute octanol–water partition coefficient (K_{ow}) and molecular weight (MW) was found to be the dominant determinant of J_{max} for this literature data set: log $J_{max} = -3.90 - 0.0190MW$ ($n = 87$, $r^2 = 0.847$, $p < 0.001$). Estimated solubility in octanol (S_{oc}) was also a determinant, but improvement in the regression by the addition of log S_{oc} was small (r^2 increased to 0.856). Addition of other physicochemical parameters to MW by forward stepwise regression only marginally improved the regression with a melting point (Mpt) term ($r^2 = 0.879$) and then hydrogen bonding acceptor capability (H_a) ($r^2 = 0.917$) is significant. Validation of the equation above was carried with a number of other data sets: an aqueous vehicle with full- and split-thickness skin ($r^2 = 0.784$, $n = 56$), some pure solutes ($r^2 = 0.537$, $n = 34$), an aqueous vehicle with ionizable solutes ($r^2 = 0.282$, $n = 54$) and solutes from a propylene glycol vehicle ($r^2 = 0.484$, $n = 36$). An analysis of the entire database gave the equation log $J_{max} = -4.52 - 0.0141MW$ ($n = 278$, $r^2 = 0.688$, $p < 0.001$), with inclusion of Mpt and H_a increasing r^2 to 0.760 ($n = 269$). Separate analysis of full- and split-thickness skin data confirmed that the dermal resistance term had only a marginal effect on overall J_{max}. Application of the latter model to an *in vivo* situation where the dermal capillary bed is slightly below the epidermal–dermal junction revealed that the dermal resistance term was unnecessary for *in vivo* predictions for most solutes.

Key words: maximum flux/prediction/structure–activity relationship/transdermal penetration
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Topical dermatological therapy is widely used to manage skin diseases. In addition, penetration of solutes through the skin may occur in environmental exposure or in applying transdermal delivery systems to treat a variety of local and systemic disorders. An important determinant of the local, systemic, or toxicological effects of a topically applied drug is its possible rate of delivery or flux, i.e., the amount of drug that can possibly penetrate the skin per unit time. The rate at which the solute is absorbed after topical exposure is related to the nature of the substance, its vehicle and the condition of the skin; the amount absorbed is a product of the rate of absorption and exposure time (Roberts and Walters, 1998).

In practice, it is the maximum flux (J_{max}) of a solute that is of most interest in determining the maximal dermal, toxic, or systemic effect. Almost all studies concerned with predicting skin permeability have focused on skin permeability coefficients (k_p, cm per h) from aqueous solutions (Scheuplein, 1967; Scheuplein *et al*, 1969; Anderson *et al*, 1988; Flynn, 1990; Potts and Guy, 1992; Pugh and Hadgraft, 1994; Abraham *et al*, 1995; Roberts *et al*, 1995, 1996, 2002; Pugh *et al*, 1996; Ghafourian and Fooladi, 2001; Vecchia and Bunge, 2002a, b). Further, if the maximal flux for a solute is known, its flux from any vehicle can be estimated using its fractional solubility in the vehicle after accounting for vehicle-induced changes in skin permeability (Roberts *et al*, 2002). Interestingly, relatively few studies have examined J_{max}-solute structure relationships using human skin data (Higuchi and Davis, 1970; Higuchi, 1978; Kasting *et al*, 1987; Roberts and Sloan, 2000; Roberts *et al*, 2002). Kasting *et al* (1987) reported that log octanol solubility (log S_{oc}) and molecular volume were significant predictors of log J_{max} for 35 compounds from saturated propylene glycol (PG) solutions through split human skin. Other determinants of J_{max} include solute molecular size (MW), octanol–water partition coefficient (K_{ow}) and melting point (Mpt) (Roberts *et al*, 2002).

In this study, we focused on collecting the published data available for human skin epidermal penetration with the goal of defining the relationship between solute J_{max} determined from experimental values and solute physicochemical prop-

Abbreviations: H_a, hydrogen bonding acceptor capability; J_{max}, maximum flux (mol per cm^2 h); K_{ow}, octanol/water partition coefficient; k_p, permeability coefficient (cm per h); Mpt, melting point (Kelvin); MV, molar volume (cm^3 per mol); MW, molecular weight (Daltons); S_{aq}, aqueous solubility (mol per mL); S_{oc}, octanol solubility (mol per mL)

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erties. We used this data to construct an extensive training database of maximum fluxes from aqueous solutions for our regression models and validated the model with experimental data for full- and split-thickness skin, ionized solutes, pure solutes, and maximum fluxes from PG. Maximum fluxes from pure solutes and PG were used as validation only, as they can affect skin permeability to different extents.

Results and Discussion

Epidermal membranes Stepwise regression of J_{max} against all physicochemical parameters for the training set identified solute MW as the main predictor (Fig 1*A, B*), according to:

$$\log J_{max} = -3.90 - 0.0190MW,\ p < 0.001,\quad n = 87,\ r^2 = 0.847 \qquad (1)$$

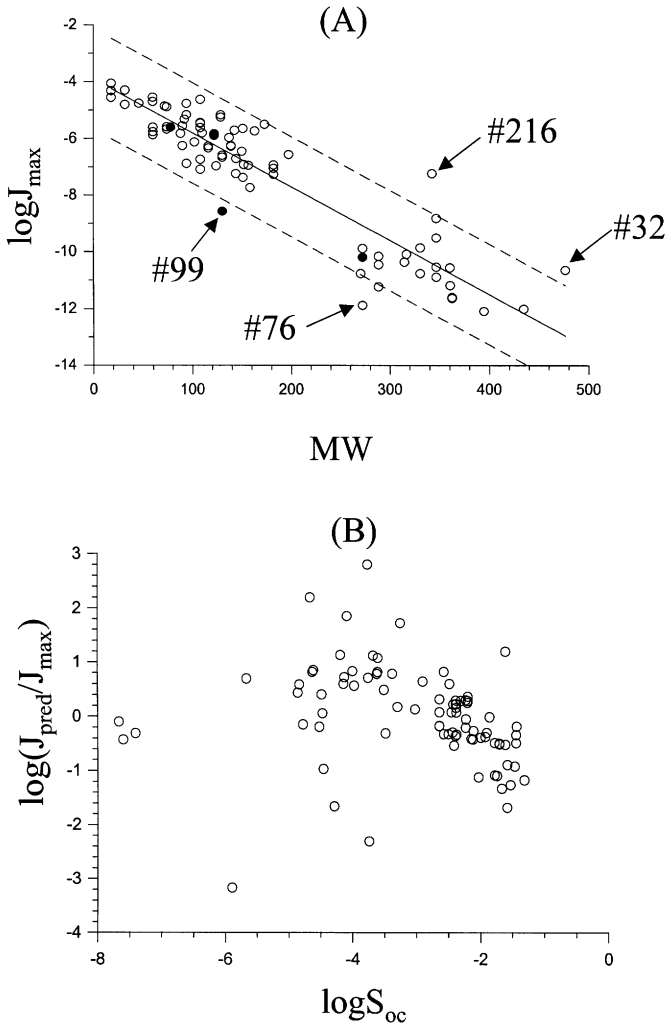

Figure 1
Relationship between J_{max} and MW and Log S_{OC}. (*A*) J_{max} values for solutes from aqueous solution through human epidermal membranes (the training set, circles), regression line based on Equation (1) using MW (solid line) and 95% confidence intervals (dashed lines). Solid symbols indicate J_{max} values obtained using saturated aqueous solutions. Most significant outliers are marked with arrows and their number in the table are given. (*B*) J_{max} values for the training set for low ($\log S_{oc} < -3.55$, circles) medium ($-3.55 < \log S_{oc} < -2.3$, box) and high ($\log S_{oc} > -2.3$, triangles) solubility in octanol.

The experimental temperature dependence, modelled as MW/T instead of MW term in Equation (1), did not considerably improve the regression ($r^2 = 0.850$). It is likely that the high inherent variability associated with the many different skin donors, experimental designs and inter-laboratory procedures for the solutes within the database swamped previously reported temperature dependency in skin transport (Scheuplein, 1967; Roberts *et al*, 1978). Log S_{oc} as a predictor alone yielded $r^2 = 0.356$. Inclusion of $\log S_{oc}$ with MW, however, slightly improved the prediction of log J_{max} over that for MW alone ($r^2 = 0.847$–0.856). The "free volume" model for diffusion of solutes within SC lipids (Kasting *et al*, 1987) is one contributor for a dependency of J_{max} on molecular size.

The maximum flux for certain series of solutes with a similar MW has been reported to be associated with a log K_{ow} of 2.5–3 and to be greatest for solutes with a low Mpt (Roberts and Walters, 1998). Stepwise regression analysis of the training data set with Mpt, log K_{ow}, and $(\log K_{ow})^2$ (Equation (4)) as well as MW confirmed MW as the main determinant of log J_{max} and showed Mpt a significant covariate (r^2 increasing from 0.847 to 0.877). Other terms in Equation (1) were not significant. Hydrogen bonding has also been recognized to be a determinant of permeability coefficients of solutes from aqueous solutions (Abraham *et al*, 1995; Potts and Guy, 1995; Pugh *et al*, 1996; Roberts *et al*, 1996; du Plessis *et al*, 2002). In stepwise regression of Equation (5) the main determinant was MW, followed by the Mp^* as a covariate and then H_a as a third covariate ($r^2 = 0.917$), with H_d having no significant effect ($\log J_{max} = -4.35 - 0.0154MW - 0.293Mp^* + 0.371H_a$). Pugh *et al* (1996) had suggested that H_a was a more significant determinant of solute diffusivity in SC lipids than solute H_d. When Equation (5) was used with a Mpt instead of Mp^* the improvement as compared with Mp^* term decreased from $r^2 = 0.879$ to 0.869 and the additional effect due to H_a from $r^2 = 0.917$ to 0.888. Mpt is a more significant covariate of J_{max} than S_{oc}, possibly reflecting SC lipids having slightly different properties compared to octanol but consistent with Mpt being a dominant determinant of solute solubility (Yalkowsky and Valvani, 1980) in SC lipids. Given that substantial variability in permeability coefficients between laboratories has previously been reported (Vecchia and Bunge, 2002b), the effect of different laboratories as a determinant of the variability of J_{max} was studied. The inclusion of laboratories (six groups; $n \geq 5$ solutes; Table S1), as a parameter, did not significantly improve the forward stepwise regression for J_{max}. In summary, the parameters which improved the model fit in addition to MW were the Mp^* and H_a.

Molar volume (MV) alone, estimated by the Fedors' group contribution method (Fedors, 1974), was a poorer predictor ($\log J_{max} = -3.53 - 0.0264MV$, $r^2 = 0.805$) than MW alone ($r^2 = 0.847$). Inclusion of log S_{oc} with MV yielded an r^2 of 0.876, whereas that for the Mp^* (Equation (5)) with MV gave an r^2 of 0.929 with the addition of H_a by stepwise regression increasing r^2 further to 0.937 ($\log J_{max} = -3.89 - 0.0180MV - 0.342Mp^* + 0.175Ha$). MV combined with Mp^* and H_a has a slightly larger r^2 ($= 0.934$) than the r^2 ($= 0.917$) for MW combined with Mp^* and H_a. We suggest that MW alone is a better predictor than MV due to higher correlation

of molecular weight with Mp^* and H_a (0.78 and 0.66) than molecular volume with Mp^* and H_a (0.62 and 0.43). This higher correlation of MW with Mp^* and H_a (which have significant contribution to J_{max}) most likely determines that MW is a better predictor of J_{max} than MV if taken alone, but MV is a slightly better determinant than MW when Mp^* and H_a contributions are already taken into account. Molar volume estimates by various methods can differ greatly. For instance, molar volumes of 31.3 cm^3 per mol and 59.6 cm^3 per mol (ethanol), 48.9 cm^3 per mol and 90.4 cm^3 per mol (benzene), 215.8 cm^3 per mol and 255.6 cm^3 per mol (hydrocortisone) were obtained with the enhanced Bondi method (Zhao *et al*, 2003) and Fedors' method (Fedors, 1974) respectively. Given the range of methods to estimate molar volume, the reported inconsistencies and arbitrary assumptions as well as solvation effects (Kharakoz, 1992; Lepori and Gianni, 2000), the readily available, simply calculated and precisely defined MW was used as the predictor of size in this work.

Given that Kasting *et al* (1987) had reported S_{oc} was a greater determinant of J_{max} for solutes from saturated PG through human skin than MW, the dominance of MW in the regression obtained for the training set in Equation (1) was unexpected. Figure 1*B* shows that, after correction for MW, no consistent pattern is evident between errors in predicting J_{max} with the molecular weight ($\log[J_{max\_predicted}/J_{max}]$) and $\log S_{oc}$ for the training set. The difference in the relative contribution of $\log S_{oc}$ and MW as predictors of $\log J_{max}$ in this work and that of Kasting *et al* (1987) may be related to solute and vehicle selection. This training set from aqueous solutions has a wider MW range of 18–477 and $\log S_{oc}$ range of -1.3 to -7.66 compared to the ranges in the data for PG of Kasting *et al* (1987) of MW 108–434 and of $\log S_{oc}$ -2.02 to -5.47. Another potential reason for the difference could be that whereas Kasting *et al* (1987) used measured values of S_{oc}, calculated values for S_{oc} ($S_{oc} = S_{aq}K_{ow}$) were used in our analysis.

Validation using full- and split-thickness skin data set Figure 2*A* shows that the J_{max} data for aqueous solutions and full- and split-thickness skin largely falls within the 95% CI obtained for SC and epidermal membranes based on MW. Analysis of the goodness of prediction of the data from Equation (1) yielded an r^2 of 0.784 ($n = 56$). Attempts to account for the additional dermal resistance by regression of full- and split-thickness skin data with J_{max} defined by Equation (7), only improved marginally overall expression for determination of J_{max}

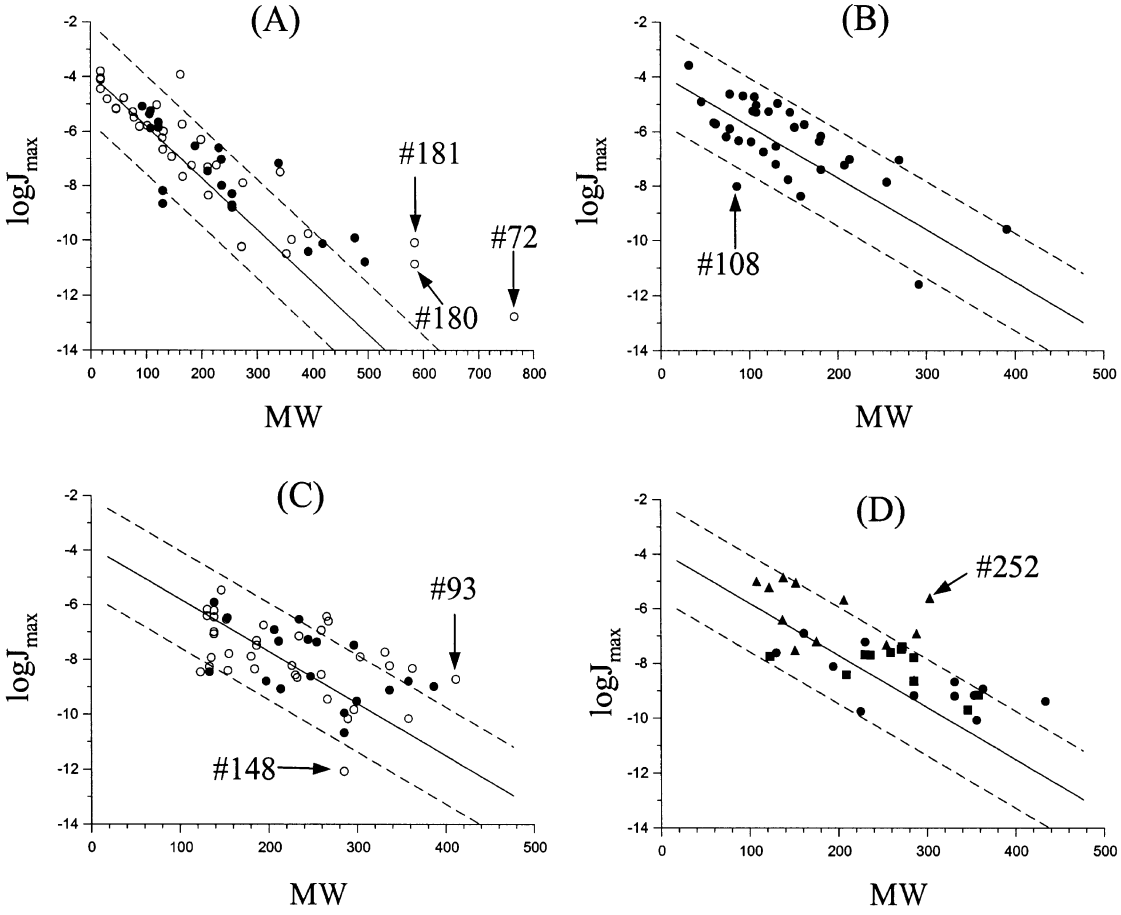

Figure 2
Relationship observed between J_{max} and MW for solute groups. J_{max} values from aqueous solutions and the full and split skin (*A*), pure liquids through human skin (*B*), ionized solutes from aqueous solutions (*C*) and from PG vehicles for low ($\log Soc < -4.6$, circles) medium ($-4.6 < \log Soc < -3.8$, box) and high ($\log Soc > -2.3$, triangles) solubility in octanol (*D*). Solid line shows prediction based on Equation (1) using MW as a predictor and dashed lines show 95% confidence intervals. Solid symbols indicate J_{max} values obtained using saturated vehicles. Most significant outliers are marked with arrows and their number in the table are given.

($n = 56$, r^2 increasing from 0.784 to 0.785):

$$\log J_{max}^{overall} = -3.90 - 0.019 \times MW - \log(1 + 10^{-1.7+1.0 \log K_{ow} - 0.019MW} \times \sqrt{MW} \times h), r^2 = 0.785 \quad (2)$$

The substances most affected by the inclusion of the dermal resistance term were those with a low MW and a high log K_{ow} (e.g., benzene, pentanol, hexanol, isoquinoline). The correction to the log J_{max} due to the dermal term does not exceed 0.34 log units for the solutes and is small compared to the average variability in the data.

For the few compounds that were poorly predicted in these thicker membranes using Equation (2) there was an underestimation of log J_{max}(predicted), contrary to intuitively expected overestimation of calculated J_{max} due to the presence of dermal resistance. One explanation could be a greater variability in the integrity of full- and split-thickness skin barrier function compared with epidermal membranes, as a range of integrity measures are usually applied to the latter. The J_{max} of digitoxin and ouabain were most noticeably higher than that predicted by Equation (1). One possible explanation for this marked deviation could be that Equation (1) only works reliably for $MW < 500$. Another possibility is that, as argued by Vecchia and Bunge (2002a, b), permeability coefficients for these two solutes are suspiciously high and should be excluded from analyses.

Validation using other data Figure 2*B* shows that most of the J_{max} data for pure solutions lie within the 95% CI obtained for the regressions based on the training set. Analysis of the goodness of fit for this data with Equation (1) yielded an $r^2 = 0.537$ ($n = 34$). Some deviations in J_{max} were expected for pure solutions as a consequence of dehydration, delipidization, solute depletion, and other direct effects on the stratum corneum (Roberts *et al*, 2002). Figure 2*C* shows that the majority of the data for the epidermal transport of aqueous ionized solutions (80%) are again within the 95% CI obtained for the regressions based on the training set. An analysis of the goodness of fit for this data with Equation (1) yielded an $r^2 = 0.282$ ($n = 54$).

Figure 2*D* shows that J_{max} for solutes in saturated solutions of PG (Kasting *et al*, 1987) also largely superimpose within the 95% CI predicted by the training set. An analysis of the goodness of fit of this data with Equation (1) yielded an $r^2 = 0.484$ ($n = 36$). The apparent slightly higher mean value for PG relative to the mean for the data in the training set is consistent with PG being a known enhancer of percutaneous absorption (Kasting *et al*, 1993). Also shown in Fig 2*D* is the effect of S_{oc} as a determinant of J_{max}. It is evident, as previously shown by Kasting *et al* (1987), that the solutes with higher solubility also generally have higher J_{max}.

Regression of complete data set Given that the validation data sets support the training set regression with Equation (1), a regression on the total data set was carried using MW as a predictor:

$$\log J_{max} = -4.52 - 0.0141MW, p < 0.001, n = 278, r^2 = 0.688 \quad (3)$$

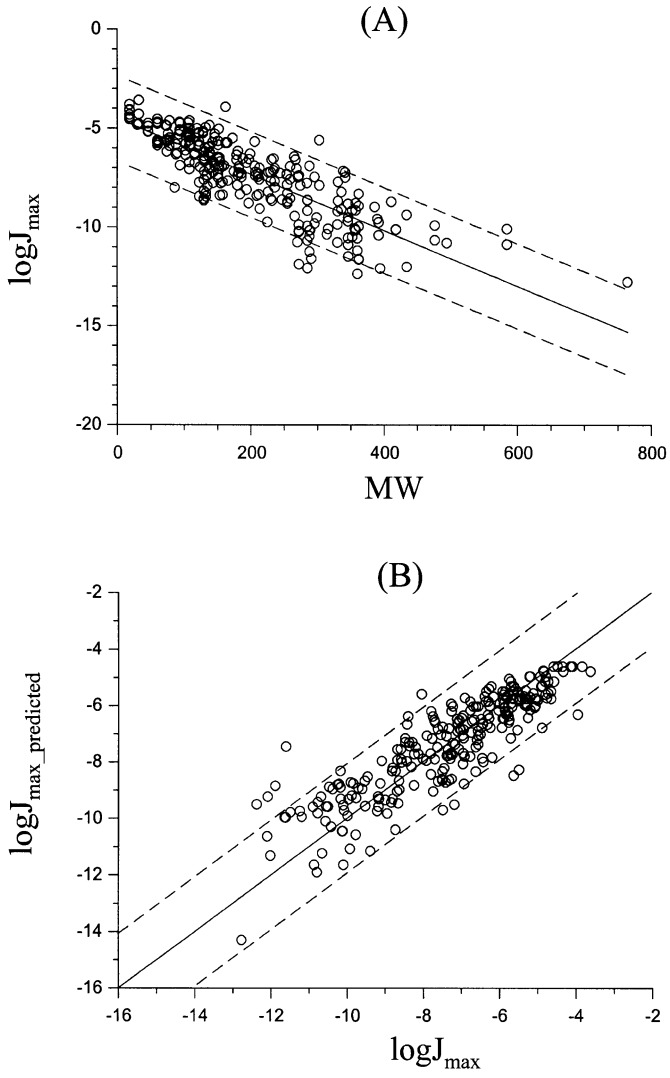

Figure 3
Prediction of J_{max} for total database. (*A*) J_{max} *versus* MW values for entire database (circles). Solid line shows prediction based on Equation (3) using MW as a predictor and dashed lines show 95% confidence intervals. (*B*) $J_{max\_predicted}$ vs. J_{max} using MW, Mp^*, and H_a. Solid line is $J_{max} = J_{max\_predicted}$, and dashed lines show 95% confidence intervals for the regression.

The result of this regression is shown in Fig 3*A*. We also performed the regression on a total database using all the predictors found significant in a stepwise regression of the training set ($\log J_{max} = -4.50 - 0.0126MW - 0.169Mp^* + 0.120H_a$, $n = 269$, $r^2 = 0.760$). All the parameters were found to be significant (MW: $p < 0.001$, Mp^*: $p < 0.001$, H_a: $p = 0.003$) and ranked in importance in the same order as for the training set (1: MW, 2: Mp^*, 3: H_a). The result of regression is shown in Fig 3*B*. It can be seen, comparing the dispersion in data in Fig 3*A* and *B*, that improvement in the prediction due to extra parameters is moderate.

Implications of the present analysis The present work suggests that MW can be used to give an initial estimate for maximum skin flux for any given solute in a saturated solution or as a pure solute. Deviations from these estimates may be anticipated for those solutions or solutes known to affect skin permeability by one of the number of

mechanisms described (Roberts *et al*, 2002). It is possible that the extent of deviation may eventually be derived from emerging enhancer–solvent property relationships. Importantly, the flux of any solute at a given concentration in a given formulation may be defined as the product of J_{max} and the fractional solubility in that formulation.

Solute MW has also been reported to be the only significant determinant of the dermal blood clearance of solutes (Singh and Roberts, 1996). Application of Equation (1) to an *in vivo* situation where the dermal capillary bed is slightly below the epidermal–dermal junction revealed that the dermal resistance term was unnecessary for *in vivo* predictions. Hence, transdermal delivery into the systemic circulation is likely to depend on MW irrespective of whether the rate-limiting step for skin absorption is diffusion through the stratum corneum or removal by dermal blood supply.

It is to be emphasized that the presented data sets are for skin penetration studies using excised human skin. As a consequence, the receptor conditions do not necessarily represent those *in vivo* provided by blood as well as the potential effects of epidermal metabolism, dermal binding or altered blood flow on epidermal penetration (Hotchkiss, 1998; Roberts and Cross, 1999) have not been considered in this analysis.

It should be recognized that there are a number of limitations associated with the predictive relationships reported in this study. The first lies in the limitation in the data available in that it does not have as much representation across the full range of all parameters as would be desirable for optimal prediction using the regression equations obtained in this work. For example, while the log K_{ow} ranges from -5.7 to $+8.7$ in Table S1, only three compounds have a log $K_{ow} > 4.5$ and 8 with a log $K_{ow} < -2$. There is clearly a need for the generation of additional data to provide a more representative range in physicochemical properties with corresponding J_{max} values to supplement that presently available in Table S1. Accordingly, the use of the present regressions to estimate J_{max} using solute physicochemical properties should be undertaken with caution. Secondly, whilst MW is the main parameter predicting J_{max}, it is to be emphasized that Mp^* and H_a are also predictors. The significance of Mp^* is most evident, for instance, for solutes with identical MW and H_a and in which the structures differ in whether one of the aromatic groups is in the *o*-, *m*- or *p*-position as illustrated by methyl 4-hydroxybenzoate (No. 146, Table S1) and methyl salicylate (No. 263, Table S1). The third limitation is the variability of data arising from studies undertaken in different laboratories, with different conditions, and on skin samples from different donors, as well as different anatomical sites. In that regard, the predicted J_{max} values are intended to be used as a guide only, and given the scatter of existing experimental data, can be expected to fall within the degree of accuracy allowable from the variability of the data set used.

Conclusion

A large amount of published data available for skin epidermal maximum fluxes have been compiled with the goal of predicting J_{max} of solutes through human skin from the solute physicochemical properties. The database set contains a diverse set of pharmacological and toxic compounds with data variability arising from different inter-laboratory procedures, skin donors, techniques, and experimental temperatures. The significance of regression models obtained is therefore, surprisingly high.

MW was found to be the main predictor of J_{max} for human skin. The prediction could only be slightly improved by inclusion of experimental temperature, Mpt, Mp^*, log S_{oc}, and H_a of the solute. This model also predicted the overall J_{max} through full- and split-thickness skin, as well as other data such as pure solutes, ionized drugs, and J_{max} from saturated PG solutions.

Materials and Methods

Database The J_{max} values of solutes and physicochemical and structural parameters used in this paper are shown in Table S1. The complete database of 278 records encompassed solutes with an extremely wide range of physicochemical properties with log K_{ow} values ranging from -5.7 to 8.7 (-3.88 to 4.52), MW varying from 18 to 765 g per mol (46–504g per mol), Mpt from 147 to 582 K (-114 to 293 K) and S_{aq} from 6.9E$-$10 mol per mL to completely miscible with water (8.0E$-$9 mol per mL to completely miscible) (in brackets the range is shown without three compounds with extreme values of the parameter at each end). The database contained results from studies performed at a range of experimental temperatures from 22°C to 39°C. J_{max} values were estimated from the product of the reported permeability coefficient (k_p) and aqueous solubility (S_{aq}) (i.e., $J_{max} = k_p \times S_{aq}$). The aqueous solubility used in the calculation of J_{max} was adjusted to the experimental temperature (Yalkowsky and Valvani, 1980; Pinal and Yalkowsky, 1988). In some cases J_{max} was available directly since the work had been done using saturated donor solution or authors reported J_{max}. The experimental and estimated physicochemical properties were also collected using Advanced Chemistry Development (ACD, Toronto, Canada) Software Solaris V4.67 (SciFinder Scholar 2001) and SRC Interactive PhysProp database. Octanol solubility was calculated as $S_{oc} = S_{aq}K_{ow}$. Molecular volume (MV) for solutes was estimated by the Fedors' (1974) group contribution method.

The database consisted of five separate data sets: (1) training set of 87 records, (2) full- and split-thickness skin set of 56 records, (3) pure liquid vehicle set of 34 records, (4) ionized solutes set of 54 records, and (5) PG vehicle set of 36 records (Kasting *et al*, 1987). These sets are designated as (Set =) t, vs, vp, vf, and vk, respectively, in Table S1. There were also 11 solutes rejected from the training set due to the lack of experimental data for the values for Mpt (Set = vm) or S_{aq} (Set = ve).

The developed training set of 64 different solutes (87 records) contains transdermal delivery data using aqueous vehicles on human skin. The inclusion criteria were that the membrane was stratum corneum (SC) or epidermis, donor and receptor fluids contained no organic liquid, the penetrant was not applied as pure liquid to the membrane, ionization was $\leq 10\%$ at the reported donor phase pH, and the experimental value for Mpt, S_{aq}, and either J_{max} or k_p was known. Theoretically based estimates of S_{aq} were deemed unsuitable for the training set as they generally use predictors such as log K_{ow} and Mpt (Roberts *et al*, 2002), which are also potential determinants of J_{max}. For those solutes where experimental values were not available, the estimated values were taken from SRC Interactive PhysProp database and used only in one of validation data sets. J_{max} values of ionized solutes were calculated from reported experimental k_p values and total solubilities given in the SRC database (which SRC advises is mainly total solubility in distilled water). Given that the available literature suggests both ionized and unionized species contribute

to observed flux (Swarbrick *et al*, 1984; Oakley and Swarbrick, 1987; Hadgraft and Valenta, 2000) and the uncertainty of pH values for the solutions used in both flux and solubility studies, no adjustments were made to correct for (1) possible differences in ionization between solutions used in penetration and in solubility studies or (2) the potential that unionized solute flux is likely to be greater than that for an ionized solute at the same solute concentration.

Data analysis J_{max} values were related to various physicochemical properties using stepwise multivariate regression analysis of various variables including the $(\log K_{ow})^2$ term adopted by Hansch and Leo (1979):

$$\log J_{max} = a - bMW - cMpt + d\log K_{ow} + d_2(\log K_{ow})^2. \quad (4)$$

Given that the solute's hydrogen bond acceptor (H_a) and donor (H_d) capacities could have effect on J_{max}, we also examined the following equation for J_{max} (modified from Roberts *et al*, (2002) with the dependence on Mpt being described using the Mpt term: $Mp^* = \Delta S_f(Mpt - T)u(Mpt - T)/T$, from Yalkowsky's solubility equation (Yalkowsky and Valvani, 1980; Pinal and Yalkowsky 1988), where ΔS_f is the entropy of fusion of a solute, u(x) is the unit step function (i.e., $u(x) = 1$ for $x > 0$ and $u(x) = 0$ for $x < 0$)):

$$\log J_{max} \approx a - bMW - c_{mp}Mp* + c_aH_a - c_dH_d + c_k \log K_{ow}, \quad (5)$$

where *T* is the experimental temperature, and a, b, c_{mp}, c_a, c_d and c_k are regression coefficients.

When the dermis provides a significant resistance in addition to the epidermis, the J_{max} can be expressed in the form of Equation (6), if it is assumed that the dermis and epidermis are a series of resistances and the J_{max} in each layer is the product of the k_p for that layer and the solubility in the vehicle.

$$J_{max} = J_{max(sc)}\left(1 + \frac{J_{max(sc)}}{J_{max(other)}}\right)^{-1}. \quad (6)$$

Equation (6) can be further simplified by assuming that the solubility in the SC is proportional to that in octanol (S_{oc}) (Kasting *et al*, 1987), that the solubility in dermis and viable epidermis ($S_{(other)}$) is proportional to that in S_{aq}, and the diffusivity in the dermis and viable epidermis($D_{(other)}$) is proportional to the inverse square root of MW (Bunge and Cleek 1995). Noting also that $K_{ow} = S_{oc}/S_{aq}$, Equation (6) becomes:

$$\log J_{max}^{overall} = \log\left[J_{max}^{epi}\left(1 + \frac{S_{(sc)}}{S_{(other)}} \times \frac{D_{(sc)}/h_{(sc)}}{D_{(other)}/h_{(other)}}\right)^{-1}\right] \cong a - bMW - \log(1 + 10^{c + d\log K_{ow} - bMW} \times \sqrt{MW} \times h), \quad (7)$$

where h is the thickness or diffusivity path length in the viable epidermis and dermis.

SPSS statistical software (SPSS Inc., Chicago, IL) (11.0 for Windows) was used for linear regression data analysis and Scientist (MicroMath Scientific Software v. 2.0) was used for non-linear regression data analysis. The dependent variable in all regressions was log J_{max}.

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Supplementary Material

The following material is available from http://www.blackwellpublishing.com/products/journals/suppmat/JID/JID22413/JID22413sm.htm
Table S1. Maximum flux and physicochemical properties data.

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Address correspondence to: Sheree E. Cross, Therapeutics Research Unit, Department of Medicine, University of Queensland, Princess Alexandra Hospital, Brisbane 4102, Australia. Email: shereec@soms.uq.edu.au

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